The role of fetal brain magnetic resonance imaging in current fetal medicine

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In this thesis the role of advanced fetal imaging in current fetal medicine was investigated. This discussion will follow the different pathologies that have come across in this manuscript: spina bifida aperta, congenital diaphragmatic hernia, cytomegalovirus infection and complicated monochorionic diamniotic pregnancies.

We investigated the use fetal magnetic resonance imaging (MRI) in patients being assessed for fetal surgery for spina bifida by, first, evaluating the reliability of MR based posterior fossa measurements around the time of spina bifida repair, second, by describing the prevalence of supratentorial anomalies and, third, by using new post-processing techniques to document brain development in the third trimester, and eventually use these to document brain changes following fetal repair. Eventually the latter techniques were used to develop a spatiotemporal atlas of the developing fetal brain in fetuses with spinal dysraphism.

First, we demonstrated that the majority of measurements that are used on postnatal MR images cannot be reliably made around the time of fetal surgery (1). These measurements include brain stem measurements (mamillopontine distance, pontine thickness, pontine length, foramen magnum diameter, level of brain stem kinking, medullar length), and foramen magnum diameter, tentorial length and cisterna magna width. Conversely, assessment of the posterior fossa dimensions and the level of cerebellar herniation were shown reproducible. The latter has been used as a secondary outcome measure in the landmark study on fetal surgery for spina bifida, i.e. the Management of Myelomeningocele Study (MOMS) study, i.e. before and after fetal surgery.

In the same study we demonstrated that already early (within 7 days) in the majority of fetuses, there is re-appearance of fluid cisterns in the posterior fossa in the vast majority of cases. Earlier studies also reported such changes between 3 and 6 weeks after the surgery in all fetuses where this was measured. The re-accumulation of intracranial cerebrospinal fluid can be an interesting proxy of the efficacy of spinal closure.

Second we described the nature and occurrence of supratentorial abnormalities in fetuses with spina bifida. Proper assessment is important for counselling women about fetal surgery and may also be relevant to parents not choosing for fetal surgery. Brain assessment is currently being used to predict the need for postnatal shunting, based on the degree of ventriculomegaly at the time of surgery. When using MRI in fetuses meeting the criteria for fetal surgery on ultrasound findings, half of them were found to have corpus callosum abnormalities and/or ventricular wall (2). This number is in line with findings in a recent systematic review by our group. Whether MRI is essential for this, hence adds information to US, has to our knowledge not been proven.

Third, we used a new 3D SVR algorithm and an automated segmentation method to document perioperative changes in fetal brain development in fetuses with spina bifida as compared to fetuses without the conditions (3, 4). Documenting in utero changes following surgery is important, as increasingly fetal surgery is being practiced, and it is expected that more of these operations will be done when minimally invasive methods will be widely implemented.

In our cohort we did not find any difference in cerebellar volume with that of controls, but demonstrated that the cerebellar shape changed importantly after fetal surgery, eventually becoming more comparable to that of controls (5). In a prior study, we have found that posterior fossa dimensions in spina bifida prior to 26 weeks, were very variable (1).

We also evaluated the white matter in our fetal surgery population, and, again, no differences in volume or shape were found compared to normal controls. These fetuses however had a variable degree of ventriculomegaly prior to fetal surgery; after the operation the ventricular width continued to increase, in concordance with the observations of others (1, 5, 6). To us, it remains unclear how the white matter volume evolves during the remainder of the pregnancy and in postnatal life in this subset of patients.

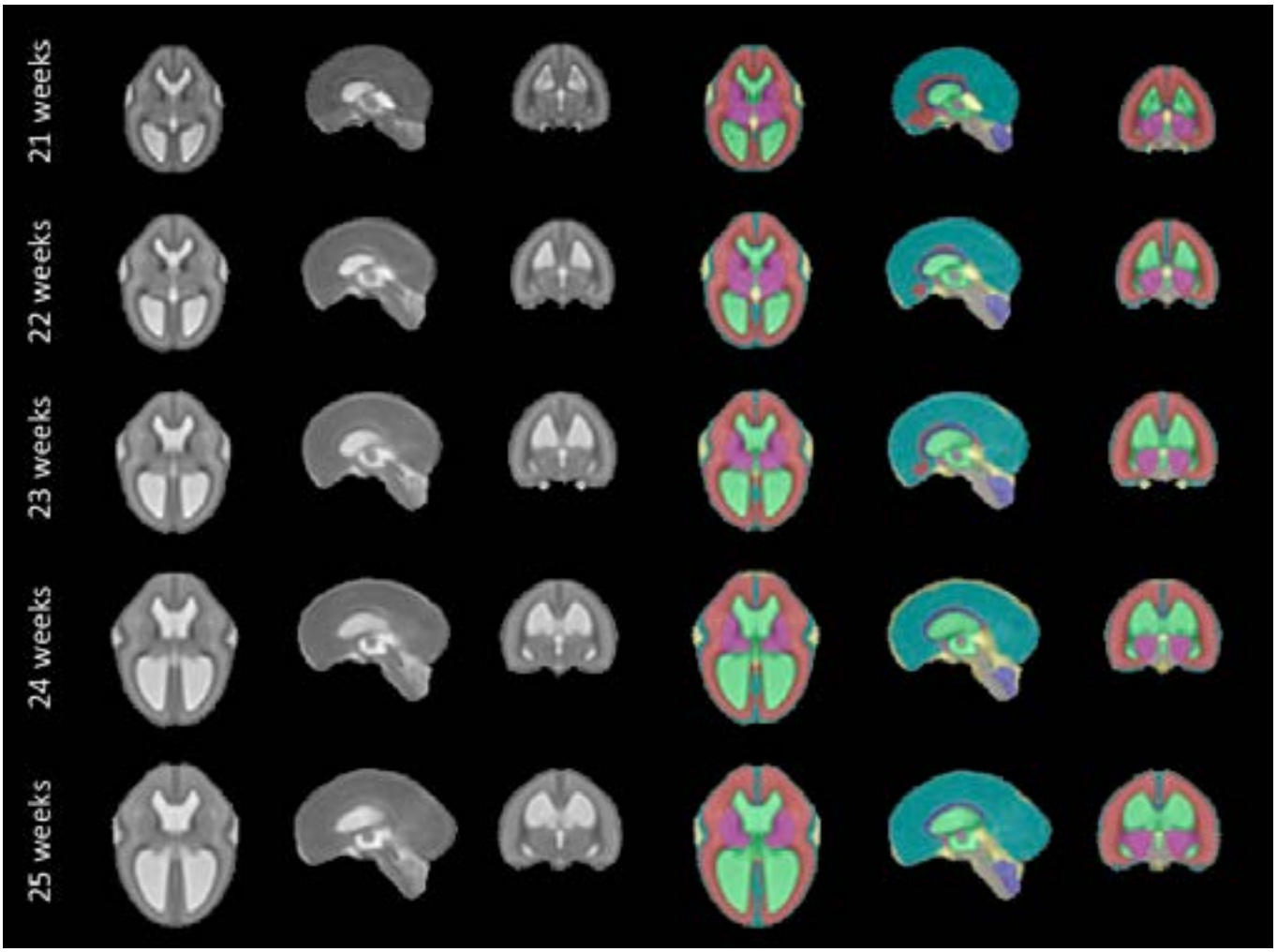
In the same study, we used spectral matching to document cortical folding. We demonstrated an increased shape index prior to fetal surgery, and a decreased shape index 7 days after fetal surgery, both compared to the index in normal controls. This is, to our knowledge, the first study specifically documenting cortical development in fetuses before and after fetal surgery (5).

Fourth, we applied the new 3D SVR algorithm to create the first spatio-temporal atlas of the fetal brain in spina bifida aperta (3, 7) (Figure 1). The application of our atlas for automated segmentation of fetal brain MRIs with open spinal dysraphism did result in a more accurate segmentation compared to those based on other atlases that used normal fetal brains.

Congenital diaphragmatic hernia (CDH) is another congenital malformation for which fetal surgery has been shown to be beneficial in given circumstances. We reported on a significant delay in brain development in fetuses with isolated CDH at 28 weeks of gestation, and to a lesser extent at 33 weeks of gestation. This is in line with earlier observations by ultrasound and the first MRI-data demonstrating an altered brain development in utero in CDH fetuses. Others have not found such differences and those looking only at postnatal data, hypothesized that postnatal events (NICU, ECMO, …) may eventually cause altered brain development.

In fetuses infected with cytomegalovirus (CMV) in the first trimester there is an increased risk of sensorineural hearing loss and impaired cognitive development. Neurosonography is the most important modality in the follow-up of fetuses with confirmed first trimester CMV-infection (8). We found an added value of fetal MRI in the third trimester in fetuses with proven first trimester CMV infection. We evaluated the routine application of diffusion weighted imaging (DWI) in fetuses with proven first trimester congenital cytomegalovirus infection (cCMV). Despite a failure rate of >10%, DWI should be implemented in routine fetal MRI for CMV. In addition, we found a significant higher apparent diffusion coefficient (ADC) value in the brain of cCMV infected fetuses compared to controls and our findings suggested a correlation with the severity of abnormalities found on anatomical sequences (9). The higher ADC is in line with a postnatal study comparing cCMV with periventricular leukomalacia in children. Moreover, they found similar findings on magnetic resonance spectroscopy, suggesting that damage and loss of oligodendrocytes are crucial factors in white matter abnormalities in cCMV infected children. This further encourages the development of a new imaging based scoring system

Figure 1: Overview of the pre-operative fetal brain in spina bifida aperta between 21 and 25 weeks of gestation with the segmentation overview. (yellow: extra-axial fluid, turquoise: cortex, red: white matter, green: intra-axial fluid, dark blue: corpus callosum, blue: cerebellum; purple: deep grey matter, grey: brain stem)



including DWI to stratify the outcome risk of fetuses after first trimester CMV infection.

In twin pregnancies, there is an increased risk of abnormal postnatal neurological development in fetuses surviving twin-twin transfusion syndrome (TTTS). Others showed a benefit of fetal brain MRI for the detection brain abnormalities in TTTS. The ISUOG practice guidelines on the role of ultrasound in twin pregnancy do not encourage fetal brain MRI at 30 weeks in survivors after laser ablation in TTTS. Nonetheless, we offer our patients a routine fetal brain MRI in the third trimester. In our retrospective study, compared to ultrasound, we found MRI is able to detect an additional brain lesion in 6% (4/69) (10). Although the number of abnormalities in our study, as in other studies, was rather small, their consequences however were very important. Of 4 such pregnancies the only one that was continued showed cerebral palsy of the affected twin postnatally. The abnormalities only detected on MRI were disorders of cortical development, known to be often missed on US and detected more easily on MRI. Our results suggest routine third trimester MRI in survivors of TTTS after laser ablation seems justified. We do feel a large prospective trial, likely multicentric, will be able to provide a complete risk assessment of these fetuses and their detected brain abnormalities.

Although we have demonstrated the added value of fetal brain MRI in several fetal conditions, it remains a challenging technique that needs to be performed upon proven indications and in centers with the necessary expertise in fetal imaging. Not only will this allow to maximize the exposure in these specialized centers, this will also permit to interpret the findings on fetal imaging (neurosonography and fetal MRI) all together in a multidisciplinary setting (including fetal specialist, radiologist, pediatric neurologist, geneticist, pathologist) as recommended.

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